Managing resistance to strobilurin fungicides

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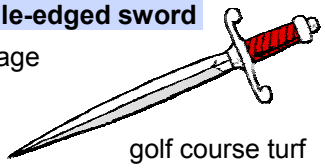
Bottom line: Resistance of anthracnose, gray leaf spot and Pythium to the strobilurin fungicides (Heritage, Compass and Insignia) has recently been documented from several U.S. golf courses. Where resistance occurs, these products are no longer effective for these three diseases. But they are still highly effective tools for control of a wide variety of other turf diseases including summer patch, brown patch, rapid blight and fairy ring. Although it is unclear how widespread the phenomenon of resistance is, implementation of preventive resistance management strategies is critical. Rotation of strobilurin products with other, unrelated fungicides appears to be the best approach for delaying development of further resistance to the strobilurins.

Effective fungicides: a double-edged sword



The 1997 introduction of Heritage (azoxystrobin) and the 1999 introduction of Compass (trifloxystrobin) for use on golf course turf was, in many ways, the start of a new and better era in turfgrass disease control. Members of a group of related fungicides known as **strobilurins,** Heritage and Compass were tested widely in research trials throughout the 1990s, and consistently demonstrated excellent activity against a broad range of turf diseases (see Table 1). The high levels of efficacy and the relatively long residual activity of these products (10 – 30 days), combined with their low toxicity to humans and the environment have made them extremely attractive to turf managers, and many previously difficult-to-control diseases, from summer patch, to rapid blight (the "chytridiomycete" disease) to brown patch, are under much better management as the result of strobilurin applications. On a global basis, sales of the strobilurin fungicides on all crops totaled $620 million in 1999, representing over 10% of the world-wide fungicide market. And azoxystrobin, the active ingredient in Heritage, had global sales of $415 million in 1999, making it the world's biggest selling fungicide (Bartlett, et. al., 2002. The strobilurin fungicides. Pest Management Science 58:649-662.)

Figure 1. *Strobiluris tenacellus* is one of several mushroom forming fungi from which the original strobilurin molecules were discovered.

But the popularity of Heritage and other strobilurins has been a double-edged sword. Because the more frequently a product is used, the more likely it is that this very same product will lose its effectiveness due to the development of **resistance**. For the turf pathogens gray leaf spot, anthracnose and Pythium, that time has unfortunately come – at least at some golf course locations. In this issue of *PACE Insights,* we will summarize what we know about resistance problems with the strobilurins and discuss strategies for delaying resistance to these important and useful products.

Table 1. Characteristics of strobilurin products available in the golf course turf market.

	GOOD LEVELS OF ACTIVITY AGAINST		
Product	**Root diseases**	**Leaf diseases**	**Comments**
Heritage (Syngenta)	summer patch, fairy ring, necrotic ring spot, spring dead spot, take-all patch	Anthracnose, brown patch, gray leaf spot, leaf spot/melting out, red thread, Southern blight	Not effective for dollar spot, rapid blight and Curvularia; weak control of Pythium. Provides systemic and activity.
Compass (Bayer)	---	Anthracnose, brown patch, Fusarium patch, gray leaf spot, leaf spot/melting out, pink snow mold, rapid blight, red thread	Not effective for dollar spot, Curvularia; weak control of Pythium. Provides primarily protective activity.
Insignia* (BASF)	summer patch	Anthracnose, brown patch, gray leaf spot, leaf spot/melting out, rapid blight, red thread	Dollar spot suppression (not control), weak control of Pythium. Curvularia not controlled. Provides primarily protective activity.

*registration expected 2003

The discovery of strobilurin chemistry

Beginning in the late 1960s, university researchers began identifying a series of substances that were produced by naturally occurring, wood-rotting, mushroom-producing fungi. These substances were classified in a group named the **strobilurins** (after one of the fungi, *Strobilurus tenacellus* (Figure 1), and were

found to be surprisingly lethal to many of the fungi that cause plant diseases.

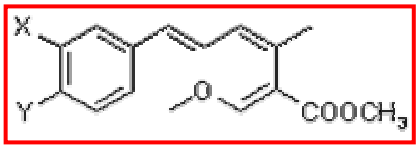
During the 1980s, several companies began work on the strobilurins, in an effort to develop them as fungicide products. Their first task was to improve the stability of the original molecules, which unfortunately broke down in a matter of seconds when they were exposed to light. As a result of these efforts, there are now several strobilurin products on the market – all with improved stability in light, and all sharing the characteristics summarized in Table 2. These light stable, commercial products, although based on the original naturally occurring strobilurin compounds, have been modified in the lab and are thus classified as synthetic chemicals, rather than as naturally occurring products.

Table 2. Characteristics shared by strobilurin products:

- Similar chemical structure (see Figure 2)
- Toxic to a broad spectrum of fungi that cause plant disease (Table 1)
- Same mode of action: kill fungi by stopping fungal energy production (in the form of ATP), thus stopping fungal spores from germinating and fungal mycelium from actively growing
- Translaminar movement: once applied, strobilurins have the ability to redistribute relatively evenly on the plant's outer surface*
- Cross resistance: if a fungus develops resistance to one strobilurin product, it will be resistant to other strobilurin products
- Low toxicity to humans and the environment

* Systemic activity, or the ability of a fungicide to move upwards inside the plant, is a feature of only one of the strobilurins registered in turf: Heritage.

Figure 2. General chemical structure shared by all strobilurin products.



Although the strobilurins as a group have many features in common, the commercial strobilurins also differ in important ways from one another, particularly in the types of diseases they control (Table 1).

Background: a definition of resistance

The turf industry has been dealing with the problem of fungicide resistance ever since the 1960s, when control failures due to dollar spot and pink snow mold resistance to benomyl were first detected. But despite our familiarity with the concept, resistance is a complex problem that is not easily understood. The definition of resistance that we will use in this article is:

Resistance occurs when turf diseases survive rates of the fungicide which would normally be lethal. This is due to a change in the disease-causing-fungus that is caused by exposure to pesticides.

The first signs of fungicide resistance begin with the observation that diseases are surviving fungicide applications, and that increased rates of product need to be applied more frequently to provide control. Eventually, the pesticide is rendered totally ineffective, regardless of the rate used.

The technical explanation for resistance

When a disease problem (for example, gray leaf spot) occurs on turf, millions of fungal spores are produced. And even though all of these spores are produced by the same fungus, they can differ from one another in many ways -- in their size, their color, their vigor. They can also differ from another in their sensitivity to a given fungicide. While most fungal spores will be killed (susceptible) to a fungicide, a few will be able to survive fungicide applications. It is these few naturally tolerant spores that are the starting point for development of resistance, as illustrated in Figure 5.

A recipe for resistance

Ingredients:

- One very effective fungicide
- One plant disease that is present for several months

Instructions:

- Rely exclusively on one fungicide
- Use this fungicide 5 - 6 times in a row
- Repeat every year

Time needed: development of resistance can occur in as little as one or two years, but it is also possible to avoid it completely. Some of the factors that influence the time needed for resistance to occur include:

Frequency of application: The more frequently you use a given fungicide, the more rapidly the events outlined in Figure 5 will occur. This is why the labels of many fungicides now contain instructions to limit the number of sequential applications to two or three per year.

Type of fungicide used: There are some fungicides, such as chlorothalonil (Daconil) or mancozeb (Fore) that, despite the fact they have been applied very frequently over a period of many years, have never caused resistance in turf diseases. This invulnerability to resistance appears to be due to the fact that these are **multi-site** fungicides – products that kill fungi by simultaneously attacking several different targets in the fungal cell. Resistance to multi-site products would require the fungus to make so many changes in its biology and genetic makeup, that it is unlikely they would all ever occur at the same time in the same fungus.

In contrast, there are other products – benomyl, thiophanate-methyl and the strobilurins – that are **single-site** fungicides. That is, they kill fungi by attacking them in only one particular spot. For the strobilurins, that spot is the Q_o site of a molecule known as cytochrome b, which occurs on the mitochondrial

membrane of fungi, and is important in the production of the energy that the fungus needs to survive. Resistance is much more likely to occur with single-site fungicides because only one change is needed in order for the fungus to be able to survive fungicide applications. In the case of the strobilurins, the change that leads to resistance is a very small difference in the makeup of the cytochrome b protein – a difference that makes it impossible for Heritage and other strobilurins to do their lethal work. When this change occurs, even extremely high rates of strobilurin fungicides have no effect on the fungal disease.

Type of disease: Some fungal diseases seem to develop resistance to fungicides more rapidly than others (see Table 3 below). The features that most resistant-prone fungi seem to share are the ability to produce many spores and/or the presence of sexual stages in their life cycles. However, there are also other characters, some of which are not understood well (including those that operate in development of dollar spot resistance), that can pre-dispose a fungus to the development of resistance.

Table 3. Turf diseases, and the likelihood that they will develop resistance to fungicides.

Resistance common	Resistance not common
• Dollar spot	• Summer patch
• Anthracnose	• Brown patch
• Pythium	• Take-all patch
• Pink snow mold	• Spring dead spot
• Gray leaf spot	• Necrotic ring spot

The strobilurin story

Although there are fungicides such as chlorothalonil and mancozeb that plant diseases have never become resistant to, these products seem to be the exception, rather than the rule. Over the years, turf plant diseases have developed resistance to a wide variety of fungicides including benomyl, fenarimol, iprodione, metalaxyl, propiconazole, thiophanate-methyl, triadimefon and vinclozolin. And starting in the late 1990s, when gray leaf spot, anthracnose and Pythium resistance to strobilurins began to cause control failures on U.S. golf courses, the strobilurin products Heritage, Compass and Insignia were added to the list. Although resistance to these three diseases does not appear to be widespread yet, the fact that it occurred only a few years after the introduction of Heritage indicates that the problem is likely to grow in the near future.

One freaky note in this story is the observation that gray leaf spot, Pythium and anthracnose resistance have occurred not only to Heritage, but also to Compass and Insignia – but years before either Compass or Insignia were commercially available (in fact, Insignia will not be available in the turf market until 2003, according to industry sources). How exactly did *this* happen? How did resistance develop to products that had never even been sprayed?

The answer lies in the concept of **cross resistance.** When a fungus becomes resistant to one fungicide, it also commonly becomes **cross-resistant** to other related fungicides that have similar chemical structures and/or similar ways of killing the fungus. Thus, Heritage-resistant anthracnose, Pythium and gray leaf spot are also cross-resistant to all other strobilurin products, because all of these compounds are chemically related to one another, and all kill fungi with the same mode of action. Cross-resistance is an unfortunate fact of life that limits the number of options available for avoiding resistance, as you will see below.

Figure 3. Application of strobilurin products to this golf course green did not prevent a serious anthracnose infestation. The likely cause of this product failure is anthracnose resistance to strobilurins.

Delaying resistance with rotation

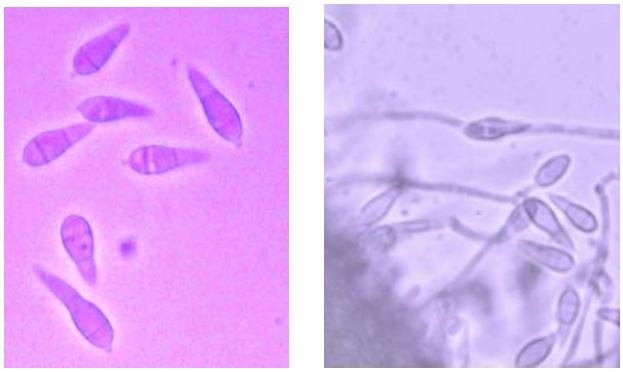
The question of how to best delay the onset of resistance is complex and also controversial. But these days, there are a few guidelines that most researchers are in agreement with:

- For products like the strobilurins, it may be impossible to completely stop resistance from ever occurring. However, it is possible to slow down the process considerably.
- Delaying the onset of resistance is something that requires preventive action – in other words you must incorporate resistance management strategies into your programs before you see signs of resistance occurring
- **Rotation** of products from different fungicide groups is probably the best way to delay the onset of resistance. Rotation is the opposite of sequential application of the same fungicide time after time. Rotation is instead a strategy that alternates the use of different and unrelated fungicides. An example of a rotation strategy for summer patch might therefore include one application with a fungicide such as Heritage, which attacks the production of energy in the fungal mitochondria – and a follow up application two weeks later with a product such as Eagle, which stops fungal growth by interrupting the production of cell membranes. By attacking the fungus on several

different fronts, rotation will make it more difficult for resistance to develop to either product.

The key to making rotation work for you is to rotate only those products that are truly different from one another – rotating Heritage with Compass, for example, would do you no good, because they are so closely related. Spraying one of these products is the same as spraying the other, at least as far as resistance management is concerned. An organization known as the Fungicide Resistance Action Committee (FRAC) has recognized the complexity of designing a rotation-based resistance management strategy, and so has organized fungicides into several different **fungicide groups** to make the task easier (Table 4). For rotation to be successful, only products from different fungicide groups should be alternated with one another.

Figure 4. Gray leaf spot (characteristic pear-shaped spores are shown in the two photos below) is one of the diseases that has easily developed resistance to strobilurin products.



Q. How widespread is resistance to strobilurin products on golf course turf?

A. At this point, confirmed cases of resistance – which involves time-consuming genetic and biological tests – have been confirmed at fewer than 20 locations in the U.S., and only for anthracnose, gray leaf spot and Pythium (Pythium resistance appears to be much less common than anthracnose or gray leaf spot at this point). The companies that produce strobilurin products have been working with golf course superintendents and university researchers to follow up and document all situations where product failures may be due to resistance, and we should be getting a clearer picture of the prevalence of the problem during the 12 months, as the testing is completed. So the answer is that at present, the extent of strobilurin resistance hasn't been quantified.

Q. How can I tell if there is strobilurin resistance at my location?

A. There is no simple test that you can conduct to determine whether the anthracnose, gray leaf spot or Pythium at your location is resistant to strobilurin products. A control failure alone is not sufficient evidence, because control failures can happen for many, many reasons, and resistance is only one possible explanation. However, if you have treated these diseases with a strobilurin product, and if you cannot explain a control failure in any other way (problems with calibration, application techniques, tank mix incompatibilities, etc), you should immediately contact your turf university extension representative and/or the company that makes the product. To investigate the possibility of resistance, samples of diseased turf will be collected from your location, and the fungi will be evaluated for the presence of changes in the fungal DNA that might lead to resistance.

Q. Which fungicide groups can be rotated with the strobilurins to help delay resistance?

A. All groups other than Group 11 (the QoI fungicides, which includes the strobilurins: see Table 4) can be alternated with the strobilurins for resistance management.

Q. If I'm using strobilurin products, how many applications should I make before rotating to a product in a different fungicide group?

A. Strobilurins are still extremely effective products and important management tools for many turf diseases. To help keep things that way, we suggest rotating to a different fungicide group after each strobilurin application is made. This means that while you may make a total of two or three strobilurin applications per year, application of products in fungicide groups other than Group 11 need to be made in between each strobilurin application.

The label instructions for Heritage and Compass are currently somewhat less conservative than we are, indicating that up to two sequential applications of these products can be made against anthracnose and/or gray leaf spot, and up to three sequential applications for other diseases. The company recommendations may change though, based on more stringent resistance management strategies that are currently under development.

Q. Will mixing two or more fungicides help to delay resistance?

A. In theory, mixtures of two products from two different fungicide groups should help delay resistance. In practice, unfortunately, it is not clear that this is the case. Although there are times when you may need to mix two fungicides together (for example, trying to control two different diseases with one application), using fungicide combinations as a resistance management strategy is usually not effective.